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In re patent application

No.	08/286,189
Applicant:	Sonia E. Sanhueza et al
Title:	INACTIVATED RESPIRATORY SYNCYTIAL VIRAL VACCINES
Filed:	August 5, 1994
Group No.	1817
Examiner:	K. Masood

18C

November 20, 1997

APPEAL BRIEF

BY COURIER

The Commissioner of Patents
and Trademarks,
BOX AF,
Washington, D.C. 20231,
U.S.A.

Dear Sir:

1. Introduction

This Appeal Brief is submitted pursuant to the Examiner's rejection for the second time on the same grounds of claims 1 to 16. (As explained below, there has been no Final Action on this case and our Notice of Appeal incorrectly refers to a final rejection of claims 1 to 16). Three copies of this Appeal Brief are being submitted. The Appeal Brief fee is included in the enclosed cheque.

2. Request for Extension of Time

Petition is hereby made under the provisions of 37 CFR 1.136(a) for an extension of four months of the period for filing this Appeal Brief. The prescribed fee is included in the enclosed cheque.

3. Real Party in Interest

The real party in interest is Connaught Laboratories Limited of 1755 Steeles Avenue West, North York, Ontario, Canada, M2R 3T4 by virtue of an Assignment from the inventors registered September 29, 1994 under Reel/Frame 7150/0232.

4. Related Appeals and Interferences

The applicants have filed an Appeal from the Final Rejection of claims 17 to 19 of copending Application No. 08/472,174, an application of which this application is the parent. Claims 17 to 19 were deleted from this application as a result of a restriction requirement. No Appeal No. has yet been notified to the applicants with respect to this appeal. The appellant, the appellant's legal representative and assignee are unaware of any additional appeals or any interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

5. Status of Claims

The application was filed with 19 claims as a continuation-in-part of Application No. 08/102,742 (now abandoned). As a result of a restriction requirement, claims 17 to 19 were withdrawn from consideration and deleted from the application. Claims 2 and 10 have been cancelled in response to the last Office Action. Claims 1, 3 to 9, and 11 to 16 are pending. The form of the claims appealed appears in the Appendix hereto.

6. Status of All Amendments filed Subsequent to Final Rejection

A first Office Action was received on this application dated October 5, 1995 and an Amendment was submitted responsive to this Office Action on April 4, 1996. A second Office Action dated July 12, 1996 issued. A response to this Office Action was filed October 3, 1996.

A third Office Action dated November 26, 1996 issued. This latter Office Action contained no notation or other indication that the Action was Final. The third Office Action indicated withdrawal of rejections of claims 1 to 16 under 35 USC 112, first paragraph, but stated:

> "Claims 1 to 16 remain rejected under 35 USC 103 for the reasons presented at pages 7 to 15 of the Office Action 7/12/96.
>
> Applicants arguments filed 10/3/96 have been considered but have not been found persuasive."

Accordingly, the claims were rejected a second time on the same ground. It is not known why the third Office Action was not made final under these circumstances. However, 37 CFR 1.191(a) permits an Appeal to be lodged from a second rejection of the claims on the same ground, even though non-Final and applicants Notice of Appeal was filed pursuant to that Rule (even though the Notice of Appeal inadvertently refers to a final rejection of claim 16 and does not specifically refer to 37 CFR 1.191(a)).

An Amendment was forwarded to the PTO by courier on April 22, 1997 and was presumably filed the following day. Since the Amendment was filed in response to a non-final Office Action, the Amendment automatically is entered and the form of the claims presented in the Appendix assumes such to be the case.

However, no further action has been received from the PTO with respect to Applicants Amendment, which applicants believe placed the application in condition for allowance. The absence of any response by the Examiner has necessitated the filing of this Appeal Brief to maintain the application pending.

7. Concise Summary of the Invention

The present invention relates to immunology and, in particular, the provision of a vaccine against infection caused by respiratory syncytial virus. The invention involves a vaccine composition capable of producing a respiratory syncytial (RS) virus specific protective immune response in a human host immunized therewith, comprising a purified inactivated RS viral preparation which is free from cellular and serum components and which is non-infectious, non-

immunopotentiating, immunogenic and protective, and a carrier therefor (page 5, lines 13 to 28; claims 1, 3 and 4). An inactivated RS viral vaccine composition which is protective and non-immunopotentiating has not previously been described.

The invention further includes a method of preparing a non-immunopotentiating, vaccine composition capable of protecting a human host immunized therewith against disease caused by infection by respiratory syncytial (RS) virus, comprising a plurality of steps. The RS virus is grown on a continuous cell line of vaccine quality. The grown virus is harvested and the harvested virus is purified under non-denaturing conditions to produce a purified virus free from cellular and serum components. The purified virus then is inactivated with an inactivating agent to provide a non-infectious, non-immunopotentiating and protective RS viral preparation, which then is formulated as a vaccine (page 4, lines 20 to 32; claims 5 to 9, and 11 to 14). In this procedure, the RS virus first is purified and then inactivated. This procedure is the key to providing a non-immunopotentiating composition.

The invention additionally includes a method of immunizing a host against disease caused by respiratory syncytial virus by administering to the host an effective amount of the vaccine composition. (page 5, line 29 to page 6, line 1; claims 15, 16).

8. Concise Statement of All Issues Presented for Review

The following prior art rejections as contained in the Office Action of November 26, 1996, are presented for review:

(a) Claims 1 to 4, 15 and 16 are rejected under 35 USC 103 as being unpatentable over Bordt et al in view of Downing et al and McIntosh et al;

(b) Claims 5 and 6 are rejected under 35 USC 103 as being unpatentable over Downing et al in view of Preston et al;

(c) Claims 5 and 9 are rejected under 35 USC 103 as being unpatentable over Downing et al in view of White et al;

(d) Claims 5, 7 and 8 are rejected under 35 USC 103 as being unpatentable over Downing et al in view of Prince et al and Georgiades et al;

(e) Claims 5, 10, 12 and 13 are rejected under 35 USC 103 as being unpatentable over Ewasyshyn et al in view of Mbiguino et al;

(f) Claim 11 is rejected under 35 USC 103 as being unpatentable over Ewasyshyn et al in view of Mbiguino et al, McIntosh et al and Paradiso et al; and

(g) Claim 14 is rejected under 35 USC 103 as being unpatentable over Ewasyshyn et al in view of Downing et al and Kuchler.

9. Grouping of Claims for Each Ground of Rejection which Applicant Contests

Insofar as multiple claims may be included in any specific rejection and to the extent such claims remain pending, the claims do not stand or fall together, but represent independently patentable subject matter.

10. Argument

(a) Background

Human respiratory syncytial (RS) virus is the main cause of lower respiratory tract infections among infants and young children. Globally, 65 million infections occur every year resulting in 160,000 deaths. In the USA alone, 100,000 children may require hospitalization for pneumonia and bronchiolitis caused by RS virus in a single year. Providing inpatient and ambulatory care for children with RS virus infections costs in excess of $340 million annually in the USA. Severe lower respiratory tract disease due to RS virus infection predominantly occurs in infants two to six months of age. Approximately 4,000 infants in the USA die each year from complications arising from severe respiratory tract disease caused by infection with RS virus and Parainfluenza type 3

virus (PIV-3). The World Health Organization (WHO) and the National Institute of Allergy and Infectious Disease (NIAID) vaccine advisory committees have ranked RS virus second only to HIV for vaccine development.

RS virus is a member of the *Paramyxoviridae* family of the pneumovirus genus. The two major protective antigens are the envelope fusion (F) and attachment (G) glycoproteins. The F protein is synthesized as a 68 kDa precursor molecule (FO) which is proteolytically cleaved into disulfide-linked F1 (48 kDa) and F2 (20 kDa) polypeptide fragments. The G protein (33 kDa) is heavily O-glycosylated giving rise to a glycoprotein of apparent molecular weight of 90 kDa. Two broad subtypes of RS virus have been defined: A and B. The major antigenic differences between these subtypes are found in the G glycoprotein.

A safe and effective RS virus vaccine is not available and is urgently needed. Approaches to the development of RS virus vaccines have included inactivation of the virus with formaldehyde, isolation of cold-adapted and/or temperature-sensitive mutant viruses and isolation of the protective antigens of the virus. Clinical trial results have shown that both live attenuated and formalin-inactivated vaccines failed to adequately protect vaccinees against RS virus infection. Problems encountered with cold-adapted and/or temperature-sensitive RS virus mutants administered intranasally included clinical morbidity, genetic instability and overattenuation.

A live RS virus vaccine administered subcutaneously also was not efficacious. Inactivated RS viral vaccines have typically been prepared using formaldehyde as the inactivating agent. Data has been reported on the immune response in infants and children immunized with formalin-inactivated RS virus. Infants (2 to 6 months of age) developed a high titre of antibodies to the F glycoprotein but had a poor response to the G protein. Older individuals (7 to 40 months of age)

developed titres of F and G antibodies comparable to those in children who were infected with RS virus. However, both infants and children developed a lower level of neutralizing antibodies than did individuals of comparable age with natural RS virus infections. The unbalanced immune response, with high titres of antibodies to the main immunogenic RS virus proteins F (fusion) and G (attachment) proteins but a low neutralizing antibody titre, may be in part due to alterations of important epitopes in the F and G glycoproteins by the formalin treatment.

Furthermore, some infants who received the formalin-inactivated RS virus vaccine developed a more serious lower respiratory tract disease following subsequent exposure to natural RS virus than did non-immunized individuals. The formalin-inactivated RS virus vaccines, therefore, have been deemed unacceptable for human use.

Evidence of an aberrant immune response also was seen in cotton rats immunized with formalin-inactivated RS virus. Furthermore, evaluation of RS virus formalin-inactivated vaccine in cotton rats also showed that upon live virus challenge, immunized animals developed enhanced pulmonary histopathology.

The mechanism of disease potentiation caused by formalin-inactivated RS virus vaccine preparations remains to be defined but is a major obstacle in the development of an effective RS virus vaccine. The potentiation may be partly due to the action of formalin on the F and G glycoproteins. Additionally, a non-RS virus specific mechanism of disease potentiation has been suggested, in which an immunological response to contaminating cellular or serum components present in the vaccine preparation could contribute, in part, to the exacerbated disease. Indeed, mice and cotton rats vaccinated with a lysate of HEp-2 cells and challenged with RS virus grown on HEp-2 cells developed a heightened pulmonary inflammatory response.

Furthermore, RS virus glycoproteins purified by immunoaffinity chromatography using elution at acid pH were immunogenic and protective but also induced immunopotentiation in cotton rats.

There clearly remains a need for immunogenic preparations, including vaccines, which are not only effective in conferring protection against disease caused by RS virus but also does not produce unwanted side-effects, such as immunopotentiation.

Art recognized approaches to the developments of RSV vaccines have been summarized in recent review articles, none of which propose the development of an inactivated RSV vaccine. Such review articles are of record in this application (submitted with April 4, 1996 Amendment).

Accordingly, for many years, the production of an RS virus vaccine has been hampered by the adverse effects produced with a formalin-inactivated RS virus in a human clinical trial conducted in the United States in the 1960's. In view of these results, the efforts of vaccine producers in the last 30 years have concentrated on the production of live attenuated RS virus mutants or subunit vaccines, rather than the use of inactivation. The various review articles of record herein relating to the RS virus quite clearly demonstrate that no consideration is being given by the at to the inactivation of virus for providing an RS virus vaccine. There is a clear prejudice in the art against using such procedure for the preparation of RS virus vaccine.

(b) Nature of the Invention

The applicants have found that, if the virus first is purified and then inactivated using β-propiolactone, ascorbic acid or octyl glycopyranoside, then a safe and effective vaccine preparation can be obtained which, in particular, elicits a protective immune response without causing enhanced pulmonary pathology (immunopotentiation). It is submitted that this procedure, the vaccine formed thereby

and the method of immunization using the vaccines are not suggested by the prior art.

(c) Rejection of Claims 1 to 4, 15 and 16 under 35 USC 103

There is some confusion as to the precise rejection made. In the Office Action of July 12, 1996, the Examiner expressed the rejection as:

> "Claims 1-4, 15 and 16 are rejected under 35 USC 103 as being unpatentable over Bordt et al in view of Downing et al and further in view of McIntosh et al"

whereas the Office Action of November 26, 1996 stated:

> "Accordingly, claims 1 to 4, 15 and 16 remain rejected under 35 USC 103 over Downing et al in view of Bordt et al and further in view of McIntosh et al." (Emphasis added).

It is presumed for the purposes of this Appeal that the Examiner intended to maintain the rejection first made. However, in view of the manner of presentation of the Examiner's remarks in the Office Action, the Argument will be presented herein with respect to the rejection as stated in the November 26, 1996 Office Action. Since the same references are employed, the rejections are essentially the same.

The claims under consideration relate to a vaccine composition containing an inactivated RS viral preparation and the use thereof in immunization. The innate prejudice in the art against inactivation of virus as a viable route to the production of a safe and effective RS vaccine has been described above.

Claim 1 defines a vaccine composition capable of producing a respiratory (RS) virus-specific protection immune response in a human host immunized therewith. The composition comprises a purified inactivated RS viral preparation which is free from cellular and serum component and which is non-infectious, immunogenic and protective, and a carrier therefor. Accordingly, the active component of the vaccine

composition, namely the RS viral preparation, is required to possess the following properties:

- purified
- inactivated
- free from cellular and serum components
- non-infectious
- non-immunopotentiating
- immunogenic
- protective

In addition, the vaccine composition containing the viral preparation is required to be capable of producing a RS virus specific protective immune response in a human host.

It is submitted that the prior art does not disclose or suggest the provision of a vaccine composition based on the RS virus nor does it provide the means to provide a RS viral preparation having the combination of properties discussed above.

In the Office Action of November 26, 1996, the Examiner indicated that the Downing et al reference teaches purification of virus free from cellular and serum components and that Bordt et al teach inactivation of "the virus" with ascorbic acid. The Bordt et al reference discloses a bovine respiratory syncytial virus inactivated with ascorbic acid, but the vaccine composition is not purified in any manner. It is clear from Example 1 of Bordt et al that the ascorbic acid is added to virus fluid to effect the inactivation and this virus fluid is not processed further in any way which would result in purification of the material. The Bordt et al material clearly is not free from cellular and serum components.

The Examiner stated in the November 26, 1996 Office Action that:

> "There was a expectation in the art regarding the use of inactivated virus before purifying the product in a vaccine composition is discussed by Downing et al (see page 216, para 1, lines 9-11)."

It is not clear where the Examiner finds support for this statement in lines 9 to 11 on page 216 and, indeed no such support exists. The Examiner has quoted the passage from page 216 of Downing et al as a whole in the Office Action, but nowhere does the passage refer to the expectation that is referred to by the Examiner. For emphasis, the passage as a whole reads:

> "one prerequisite for systematic biochemical and functional analysis of viruses is an abundant and very pure viral preparation, preferably one with infective virus particles. The efficient and effective purification schemes for enveloped viruses are important both clinically and for many research efforts especially for the development of strategies for disease intervention, particularly where traditional vaccines have not worked well. Respiratory syncytial virus (RSV) is an example of an enveloped virus from the class of paramyoxoviridae. RSV causes respiratory infection that is both difficult to treat and is not currently amenable to prevention by vaccination."

This passage clearly refers to the problems of a traditional vaccine strategy for RS virus infection and the need for the development of strategies for disease intervention, that is therapeutic treatment of infection, rather than prevention of the disease by vaccination, since it is indicated by Downing et al this is not possible by traditional means. The whole thrust of Downing, therefore, is to provide an affinity purification method for RSV using a specific material to provide purified virus to carry out the studies which are referred to in the first paragraph of the Downing et al reference, i.e., to develop strategies for disease intervention. Downing provides no motivation whatsoever to provide an inactivated RS viral preparation for vaccine use

and, indeed, Downing indicates that traditional vaccination routes for RSV infection have not been successful.

The Examiner further stated in the November 26, 1996 Office Action:

> "Formalin-inactivation caused disease potentiation partly due to the action on the F and G glycoproteins and impure viral preparation containing cellular or serum components (see page 3, para 3, lines 5-10 of the last Office Action)."

There is no paragraph 3 on page 3 of the Office Action of July 12, 1996. The rejection of claims 1 to 4, 15 and 16 is contained on page 8 and 9 of the Office Action of July 12, 1996. There is no discussion of formalin inactivation and the effects thereof in this passage. Accordingly, the basis of the Examiner's comment is obscure.

The Examiner further stated in the November 26, 1996 Office Action:

> "Downing et al also addresses the issue why vaccines have not worked in the past partly due to impure viral preparation (see introduction section)."

Downing et al does not in any way address why vaccines have not worked in the past. What the introductory portion of the Downing et al reference states is that traditional routes of vaccination against RSV viral infection have not been successful and that it is necessary to produce pure viral preparation for the purpose of carrying out systematic studies on the virus with a view to the development of strategies for disease intervention. Downing et al does not in any way contemplate a traditional means of preventing disease caused by RS viral infection, since Downing et al and, indeed others in the art as noted by the above discussion of the prejudice in the art, simply did not believe that it would be possible to provide an inactivated RSV preparation which would be effective.

The Examiner further stated in the Office Action of November 26, 1996:

> "One of ordinary skill in the art would be motivated to purify the virus first to remove contaminants as suggested by Downing et al then inactivate the virus with the ascorbic acid or other inactivating agent that has been used traditionally in the virology field. One of ordinary skill in the art would have expected that by purifying the virus first then inactivation of virus would be more efficacious since there is no contaminants."

It is submitted that there is no such motivation provided by the prior art. The only motivation provided by Downing et al is the provision of a process of purifying RS virus for the purpose of studying its biology for the purpose of the development of a strategy for disease intervention for a disease where traditional vaccination methods have been ineffective. The only motivation provided by Bordt is the realization that ascorbic acid may be used for inactivation of various viral preparations, one example of which is bovine RSV. However, the preparation of such inactivated materials does not involve any purification, as is evident from Example 1 of the Bordt et al reference.

Absent the hindsight of the present invention, there is absolutely no basis for the assertion made by the Examiner in the last paragraph of the above quotation. There is no suggestion whatsoever, in the prior art that has been relied on, that one would first purify the virus and then inactivate it with the expectation of obtaining a more efficacious vaccine.

The Examiner stated in the November 26, 1996 Office Action that:

> "McIntosh was incorporated to as evidence that one of ordinary skill in the art would have been motivated and expected to inactivate 'human RSV' as set forth in the first Office Action (see page 9, first paragraph).

While McIntosh et al teach that human RSV is the most important cause of viral lower respiratory tract disease in infants and children, and that human RSV is a paramyxovirus,

it is not seen in what way these observations are relevant to the patentability of applicant's claims. It is not seen where, in the first paragraph on page 9 of the first Office Action, or indeed in the last Office Action, there is basis for the quotation "human RSV", as stated by the Examiner.

It is clear from the above comments that the applicants vaccine composition of claim 1 and method of immunizing defined in claim 15 are clearly patentable over the teachings of the combination of Downing et al, Bordt et al and McIntosh et al, however the references are ordered.

Claims 3 and 4 relate to specific forms of the vaccine composition. Claim 3 recites that the carrier further comprises an adjuvant while claim 4 recites that the composition is formulated to be administered in an injectable form, intranasally, orally, or to mucosal surfaces. While such formulations are convenient ones to vaccines, the Examiner is wholly silent with respect to such features.

Claim 16 is dependent on claim 15. As has already clearly been demonstrated, there is no disclosure or suggestion to effect immunization of a host against RSV by using an inactivated virus preparation. Claim 16 recites the host to be selected from hosts commonly susceptible to RS virus infection. Again, while this is well known, the Examiner makes no specific comment with respect to such claim.

It is clear, therefore, that claims 1 to 4, 15 and 16, insofar as they remain in the application, are patentable over the applied art and the rejection thereof under 35 USC 103 as being unpatentable over Bordt et al in view of Downing or Downing in view of Bordt et al and further in view of McIntosh, should be reversed.

(d) Rejection of Claims 5 and 6

Claims 5 and 6 are rejected under 35 USC 103 as being unpatentable over Downing et al in view of Preston.

Claim 5 defines a method of preparing a non-immunopotentiating vaccine composition capable of protecting a

human host immunized therewith against disease caused by infection by respiratory syncytial virus by effecting a plurality of defined steps. These steps include growing RS virus on a continuous cell line of vaccine quality to produce a grown virus, harvesting the grown virus to produce a harvested virus, purifying the harvested virus under non-denaturing conditions to produce a purified virus free from cellular and serum components, inactivating the purified virus with an inactivating agent to provide a non-infectious non-immunopotentiating and protective RS viral preparation and formulating the non-infectious, non-immunopotentiating and protective viral preparation as a vaccine.

The teachings of Downing et al and their relevance to applicant's invention are discussed above in connection with the first prior art rejection. As pointed out earlier, the Downing et al reference does not teach inactivating any virus with any inactivating agent and there is prejudice in the art against inactivating virus for the purpose of providing vaccine compositions in view of the problems associated with such inactivation using formalin, the most common inactivating agent used in the preparation of vaccines.

The Downing et al reference describes a procedure for preparing pure RS viral preparation for the purpose, as already noted, of assembling knowledge of the basic biology of the virus for the development of strategies for disease intervention. The Downing et al reference says nothing about the preparation of vaccine compositions and, indeed, is concerned with an ultimate goal of a strategy for disease intervention because traditional vaccination does not work.

The purpose of the Preston study was to understand the immune response relating to the reduced resistance of subsequent RSV infections, by in-vitro studies aimed at inhibiting the proliferative T-cell response to inactivated RSV. The purpose of the β-propiolactone used in this study was to prepare inactivated RSV to be used only to stimulate

the adult mononuclear cells for the purpose described above. There is no preparation of a vaccine composition that is contemplated by Preston. While, as the Examiner stated in the Office Action of November 26, 1996, Preston et al teaches that β-propiolactone is effective in inactivating RSV, nevertheless, this disclosure provides no motivation whatsoever to inactivate a virus for a vaccine composition for the same reasons that the Bordt et al reference provides no motivation for inactivation of pure virus for vaccine preparation, since the Downing et al reference, in fact, points away from vaccination as a means of controlling RS viral infection and, in fact, is concerned with strategies for disease intervention and not vaccination.

In the Office Action of November 26, 1996, the Examiner stated:

> "One of ordinary skill in the art would inactivate a virus for an immunogenic composition to prevent the host from being infected with the virus despite it inhibits the T cell response and reduce resistance to RSV. Applicants arguments are noted. The Examiner acknowledges RSV response is inhibited by infectious RSV. However in a vaccine where the response is prior to infection the issue of infectious RSV inhibiting RSV-response of an inactivated RSV would not have been expected using β-propiolactone for vaccination. Therefore, applicants arguments regarding the different purpose of Preston study i.e. to inhibit the proliferative T-cell response to inactivated RSV is moot".

However, the prejudice in the art against basing a RS virus vaccine on inactivated virus has been well developed above. The Examiner's comments ignore such prejudice. It is submitted that the prior art nowhere discloses or suggests the specific combination of steps of claim 5, including <u>first</u> purifying and <u>then</u> inactivating the purified virus and then <u>formulating</u> the inactivated RS viral preparation as a vaccine.

Claim 6 is dependent on claim 5 and recites that the inactivating agent is β-propiolactone. While Preston

specifically describes β-propiolactone, there is no suggestion, for the reasons discussed in detail above, in the cited prior art, to employ β-propiolactone as an inactivating agent in a procedure of forming a vaccine composition for protecting human hosts.

Accordingly, claims 5 and 6 are patentable over the applied art and hence the rejection of claims 5 and 6 under 35 USC 103 as unpatentable over Downing in view of Preston et al, should be reversed.

(e) Rejection of Claims 5 and 9

Claims 5 and 9 are rejected under 35 USC 103 as being unpatentable over Downing in view of White et al.

As the Examiner noted in the November 26, 1996 Office Action, White et al teaches inactivation of RSV by treatment with ascorbic acid. The purpose of the study reported by White et al was to determine the in vitro effect of ascorbic acid on viruses and to use the inactivated virus as a reagent in serologic assays, and not for the production of inactivated RSV vaccine. The Examiner stated in the November 26, 1996 Office Action that:

> "Applicants arguments are not commensurate with the claimed invention. The claimed invention is not drawn to inactivation as a vaccine."

Claim 5 was amended in this respect and specifically refers to production of a vaccine.

The Examiner stated in the November 26, 1996 Office Action:

> "Further in view of inactivation with ascorbic acid is useful for serological assays wherein this antibody-antigen reaction it would have been reasonable for one ordinary skilled in the art to expect to use ascorbic acid for vaccination wherein an antigen-antibody reaction takes place."

It is submitted that the study reported by White and on which the Examiner relies provides no basis for any expectation with respect to an antibody response in a host to which is

administered the RS viral vaccine composition of the present invention.

The Examiner further stated in the Office Action of November 26, 1996:

> "Furthermore, applicants arguments of not yielding a preparation free of cellular contaminants are not persuasive because the claimed invention is not commensurate with the scope of the claims. The claimed invention only recites virus "substantially" free from cellular and serum components."

In this regard, while not necessarily agreeing with the Examiner's position, applicants amended claim 5 and also claim 1 to delete the term "substantially" in response to the Office Action.

In White, the infected cells are grown in roller bottles, scraped, disrupted by a freeze-thaw cycle and further clarified by centrifugation. This procedure of virus purification would not yield a viral preparation free of cellular contaminants as required by applicant's claims.

As already pointed out above, the Downing et al reference provides no motivation whatsoever for consideration of inactivation of virus, whether purified or not, as a route to providing an effective RS virus vaccine, since the whole thrust of Downing et al is to provide a pure viral preparation for the purposes of assembling knowledge of the basic biology of the viruses and developments of strategies for disease intervention. Accordingly, the combination of art lacks any motivation whatsoever, to use ascorbic or any other material for inactivation of purified RS virus.

Claim 9 is dependent on claim 5 and recites that the inactivation is effected using ascorbic acid. While White et al describe ascorbic acid, there is no suggestion, for the reasons discussed in detail above, in the cited prior art, to employ ascorbic acid as an inactivating agent in a procedure of forming a vaccine composition for protecting human hosts.

Accordingly, it is submitted that claims 5 and 9 are patentable over the art and hence the rejection of claims 5 and 9 under 35 USC 103 as being unpatentable over Downing in view of White et al, should be reversed.

(f) Rejection of claims 5, 7 and 8

Claims 5, 7 and 8 are rejected under 35 USC 103 as being unpatentable over Downing et al in view of Prince et al and Georgiades et al.

The Downing et al reference and the motivation provided thereby have been discussed above in connection with other prior art suggestions. The Prince et al reference relates to the use of non-ionic detergents to sterilize blood plasma, so as to be free of active hepatitis virus. Hepatitis is a DNA virus belonging to the hepadnaviridae family of viruses, while RSV is a negative strand RNA virus belonging to the paramyxoviridae virus family. The conditions found suitable for inactivating viruses belonging to the hepadnaviridae family of viruses may not be suitable for viruses belonging to the paramyxoviridae family. In the Prince et al reference, it is recommended that a combination of a non-ionic detergent, alcohol or ether, or a mixture of both, be used to inactivate hepatitis viruses during plasma processing. Detergent alone is used in the present application to inactivate RSV.

The Examiner stated in the Office Action of November 27, 1996 that:

> "While it is true Prince et al teach inactivation of the hepatitis virus with non-ionic detergents ... since Downing et al suggest the use of non-ionic detergents including octyl glucoside for solubilization of viral preparation of VSV ... it would have been expected non-ionic detergents would have inactivated the RS virus for the preparation of vaccine composition."

In the section to which the Examiner refers in Downing et al, on page 218, it is stated that octyl glucoside was used to solubilize proteins from VSV (vesicular stomatitis virus) and

the VSV G protein was isolated. It is unclear how this teaching leads to any expectation from the Prince et al disclosure that any non-ionic detergent may be used for inactivation of RS virus.

The Georgiades et al reference is concerned with a process for the purification of interferon alpha and to a method of enhancing the overall recovery of interfon alpha. The purpose of using the detergent in the reference was to eliminate virus contamination and not to produce inactivated viral preparations. The Examiner stated in the November 26, 1996:

> "Further while it is true that Prince et al teach inactivation of plasma hepatitis virus and Georgiades et al teach inactivation of contaminating viruses by non-ionic detergents respectively, one of ordinary skill in the art would have been motivated and expected to use non-ionic detergents when the virus is first purified as suggested by Downing et al."

It is submitted that there is absolutely no justification in the combination of prior art for this assertion. It has already been pointed out the manner in which the Downing et al reference specifically points away from the use of viral preparations as a means of controlling respiratory syncytial virus disease, the whole purpose of the preparation of the purified virus in Downing et al being to assemble knowledge of the basic biology of the virus and the development of strategies for disease intervention and not for any vaccine. The secondary references merely point to the potential for inactivating various viruses using non-ionic detergents and there is no motivation whatsoever contained in these teachings to utilize a non-ionic detergent for the inactivation of RS virus following the steps of growing, harvesting and purifying the virus, as required by applicant's claim 5, nor is there any suggestion for subsequent formulation of the inactivated viral preparation as a vaccine, also as required by applicants claim 5.

Claims 7 and 8 are dependent on claim 5 and recite that the inactivating agent is a non-ionic detergent (claim 7), which may be n-octyl-α-D-glucopyranoside or n-octyl-β-D-glucopyranoside (claim 8). The suggestions to use non-ionic detergents and specific non-ionic detergents to inactivate various viruses, but not apparently RS virus, do not in any way overcome the innate prejudice in the art with respect to the use of virus inactivation in a procedure of forming a vaccine composition for protecting human hosts against RS virus infection.

Accordingly, it is submitted that claims 5, 7 and 8 are patentable over the applied art and, hence the rejection thereof under 35 USC 103 as being unpatentable over Downing et al, Prince et al and Georgiades et al, should be reversed.

(g) Rejection of Claims 5, 10, 12 and 13

These claims have been rejected under 35 USC 103 as being unpatentable over Ewasyshyn et al in view of Mbiguino et al. Of these claims, claim 10 has been deleted and claim 12 was amended to an independent form in response to the Office Action of November 26, 1996.

The Ewasyshyn et al reference describes the production of purified surface glycoproteins of RSV and PIV-3. The only similarity or relevance to the present invention is that both the present invention and Ewasyshyn et al describe growing and harvesting of RS virus. Thereafter, the processes diverge significantly. In the present invention, the harvested whole virus is further processed through the steps of purification, inactivation and formulation, while Ewasyshyn et al then solubilize and isolate glycoproteins from the harvested virus. There is no teaching in Ewasyshyn et al of inactivation of virus because the Ewasyshyn et al procedure extracts the surface glycoproteins from the virus and is concerned solely with processing that extracted material to isolate the glycoproteins.

The Ewasyshyn et al reference, therefore, describes a method of preparing materials for a subunit RS virus vaccine. The Ewasyshyn et al reference is wholly silent with respect to the potential use of the whole virus as the basis for a vaccine composition.

The Mbiguino et al reference is concerned solely with a procedure for purifying RS virus and compare the use of sucrose gradient purification with percol, renografin and metrizamide for purification. The protocol utilized by Mbiguino et al is illustrated diagramatically in Figure 1 of the reference. There is no inactivation step which is carried out in Mbiguino et al.

It is submitted that the combination of Ewasyshyn et al and Mbiguino does not disclose or suggest applicants method as defined in claim 5 and particularly, the method defined in claim 12. Claim 5 defines a method of preparing a non-immunopotentiating, vaccine composition capable of protecting a human host immunized therewith against disease caused by infection by RS virus. The combination of steps recited comprises growing and harvesting the virus, both of which steps are described in Ewasyshyn and Mbiguino. Applicants then purify the harvested virus under non-denaturing conditions to provide a purified virus free from cellular and serum components. The Examiner conceded in the November 26, 1996 Office Action:

> "The Examiner acknowledges Ewasyshyn et al does not teach of purifying the virus. However in view that Mbiguino et al teaches of a new method to obtain substantial amounts of purified RSV, one of ordinary skill in the art would have been motivated to use the method as set forth in Mbiguino et al."

There is no reason to apply the teachings of Mbiguino et al to Ewasyshyn et al since the purpose of Ewasyshyn is to produce purified surface glycoproteins of RSV and PIV-3 by extraction of the glycoproteins and subsequent co-purification of the extracted proteins. It is not clear why one would apply any

teachings of Mbiguino et al to the clear and limited teaching of Ewasyshyn et al.

The Examiner further commented in the November 26, 1996 Office Action:

> "Mbiguino et al teaches an inactivation by using non-ionic detergent conditions using a sucrose gradient."

Nowhere does Mbiguino et al refer to inactivation of the virus and, indeed, this would appear to be counter-productive to the procedure which is employed by Mbiguino et al, who is attempting to obtain purified virus preparations with high titres (see Summary). There is no description in Mbiguino et al of the "non-ionic detergent conditions" to which the Examiner refers.

Applicants had previously pointed out that the Mbiguino et al purification method is not for vaccine development. The Examiner stated in the Office Action of November 26, 1996:

> "Applicants arguments are noted. However applicants arguments are not persuasive since the claims are not drawn to a vaccine but an immunogenic composition."

It is noted that applicants claims are directed to the preparation of vaccines, in the amended form presented in response to the November 26, 1996 Office Action. The Examiner further stated in the November 26, 1996 Office Action:

> "Since this method [i.e., Mbiguino et al] preserves viral infectivity would be expected the composition would be immunogenic as the claimed invention recites."

The indication that preservation of viral infectivity also clearly demonstrates that there is no inactivation step described or contemplated by Mbiguino et al.

Following the purification step, applicants inactivate the purified virus with an inactivating agent to provide a non-infectious, non-immunopotentiating and

protective RS viral preparation and then formulate the non-infectious, non-immunopotentiating, protective RS viral preparation as a vaccine. Neither Ewasyshyn et al nor Mbiguino et al suggest any such inactivation and formulation steps.

In the specific procedure defined in independent claim 12, the purification step is defined as a combination of microfiltration to remove cell debris, tangential flow ultrafiltration to remove serum components and provide a retentate, pelleting the retentate by ultracentrifugation to further remove serum components and then subjecting the pelleted material to sucrose gradient centrifugation. It is submitted that this specific combination of steps is not taught or suggested by the prior art relied on.

Claim 12 also recites the inactivation of the purified virus with an inactivating agent which is selected from the group consisting of β-propiolactone, a non-ionic detergent which is n-octyl-α-D-glycopyranoside or n-octyl-β-D-glycopyranoside, and ascorbic acid. It is submitted that, not only is inactivation not disclosed in either reference relied on in rejection of this claim, but also none of the specific materials recited in claim 12 are described or suggested for such purpose in the applied combination of prior art.

Claim 13 is dependent on claim 12 and recites a specific molecular weight cut-off membrane for effecting the tangential flow ultrafiltration step. Since neither Ewasyshyn et al nor Mbiguino et al alone or in combination describe applicants combination of purification steps, it follows that the prior art also does not disclose the features of claim 12.

Accordingly, it is submitted that claims 5, 10, 12 and 13, insofar as they remain in the application, are patentable over the applied art and hence the rejection of claims 5, 10, 12 and 13 under 35 USC 103 as being unpatentable

over Ewasyshyn et al in view of Mbiguino et al, should be reversed.

(h) Rejection of claim 11

This claim, which is dependent on claim 5 and is directed to the use of a VERO cell line as the continuous cell line of claim 5, is rejected under 35 USC 103 as being unpatentable over Ewasyshyn et al in view of Mbiguino et al and further in view of McIntosh et al and Paradiso et al.

The McIntosh and Paradiso et al references both describe the use of VERO cells for growing RS virus. However, it has already been pointed out the manner in which the combination of Ewasyshyn et al and Mbiguino et al is deficient with respect to potential rejection of claim 5. None of these deficiencies is made up by the McIntosh and Paradiso et al references. In particular, it is submitted that the combination that has been made in no way discloses or suggests applicants specific combination of process steps as defined in claim 5.

Accordingly, it is believed that claim 11 is patentable over the art and hence the rejection of claim 11 under 35 U.S.C. 103 as being unpatentable over Ewasyshyn et al in view of Mbiguino et al and further in view of McIntosh et al and Paradiso et al, should be reversed.

(i) Rejection of claim 14

Claim 14 is rejected under 35 USC 103 as being unpatentable over Ewasyshyn et al in view of Downing et al and Kuchler.

Claim 14 was amended into independent form in response to the Office Action of November 26, 1996. In the purification procedure recited in claim 14, the specific steps include microfiltration to remove cell debris, tangential flow ultrafiltration to remove serum components, gel filtration to further remove serum components, and ion exchange chromatography to additionally remove serum components. It is

submitted that the specific combination of steps is not taught nor suggested by the prior art relied on.

The disclosure of the Ewasyshyn reference has been discussed above. As noted herein and as conceded by the Examiner, the Ewasyshyn et al reference does not disclose purification of the virus and hence it cannot describe applicant's specific combination of process steps for such purpose as recited in claim 14. In addition, the Ewasyshyn et al reference fails to recite or suggest inactivation of RS virus, nor the formulation of inactivated RS virus as a vaccine composition. The Ewasyshyn et al reference is solely concerned with the isolation and purification of specific glycoproteins from the RS virus for use in a subunit approach to the RS virus vaccines.

The Downing et al reference, it is submitted, adds nothing to the Ewasyshyn et al reference other than the provision of a purified form of the RS virus. The purpose for generation of this material by Downing et al has been discussed in some detail above in connection with the rejections which are based on Downing et al. It is considered unnecessary to repeat those discussions here. Suffice it to say that the preparation of the purified RS virus in Downing et al was for the purpose of assembling knowledge of the basic biology of the virus and development of strategies for disease intervention. Downing et al does not describe or suggest any inactivation step, as already conceded by the Examiner.

In the November 26, 1996 Office Action, the Examiner indicated that the Kuchler teachings had been described in the prior Office Action. In this regard, the Office Action of July 12, 1996 recites:

> "Kuchler teaches that there are three basic steps to the purification of viruses (p. 184-194). The first is clarification (p.185). The second is concentration which may be performed by several methods including ultrafiltration (p.185). The third step is purification. Kuchler teaches that purification of viruses may be accomplished by

> chromatograph and ion-exchange resins, by molecular sieving on gel filtration columns, by countercurrent distribution or by gradient centrifugation (p.186, paragraph 4)."

The Kuchler reference, therefore, simply contains a general teaching of the steps involved in purification of viruses and describes the use of various materials for such purification. It is submitted that this disclosure falls far short of applicants recited combination of process steps in claim 14, as discussed above, in the preparation of a vaccine composition.

As already pointed out, the combination of Ewasyshyn and Downing is deficient in failing to disclose or suggest an inactivation step and formulation of the inactivated virus as a vaccine and the Kuchler reference provides no remedy to this particular defect.

Accordingly, it is apparent that claim 14 is patentable over the art, and hence it is submitted that the rejection of claim 14 under 35 U.S.C. 103 as being unpatentable over Ewasyshyn et al in view of Downing et al and Kuchler, should be reversed.

11. Summary

It will be seen from the discussion above that all applicants pending claims are patentable over the art and hence the various grounds of rejection of the claims under 35 USC 103 as being unpatentable, should be reversed.

Respectfully submitted,

M.I. Stewart

Michael I. Stewart
Reg. No. 24,973

Toronto, Ontario, Canada
(416) 595-1155
FAX No. (416) 595-1163

APPENDIX

CLAIMS APPEALED

1. A vaccine composition capable of producing a respiratory syncytial (RS) virus specific protective immune response in a human host immunized therewith, comprising a purified, inactivated RS viral preparation which is free from cellular and serum components and which is non-infectious, non-immunopotentiating, immunogenic and protective, and a carrier therefor.

3. The composition of claim 1 wherein said carrier further comprises an adjuvant.

4. The composition of claim 1 formulated to be administered in an injectable form, intranasally, orally, or to mucosal surfaces.

5. A method of preparing a non-immunopotentiating, vaccine composition capable of protecting a human host immunized therewith against disease caused by infection by respiratory syncytial (RS) virus, which comprises:

growing RS virus on a continuous cell line of vaccine quality to produce a grown virus;

harvesting said grown virus to produce a harvested virus;

purifying said harvested virus under non-denaturing conditions to produce a purified virus free from cellular and serum components;

inactivating said purified virus with an inactivating agent to provide a non-infectious, non-immunopotentiating and protective RS viral preparation, and

formulating said non-infectious, non-immunopotentiating and protective RS viral preparation as a vaccine.

6. The method of claim 5 wherein said inactivating agent is β-propiolactone.

7. The method of claim 5 wherein said inactivating agent is a non-ionic detergent.

8. The method of claim 7 wherein said non-ionic detergent is selected from the group consisting of n-octyl-α-D-glucopyranoside and n-octyl-β-D-glucopyranoside.

9. The method of claim 5 wherein said inactivating agent is ascorbic acid.

11. The method of claim 5 wherein said continuous cell line is a VERO cell line.

12. A method of preparing a non-immunopotentiating vaccine capable of protecting a human host immunized therewith against disease caused by infection by respiratory syncytial (RS) virus, which comprises:

growing RS virus on a continuous cell line of vaccine quality to produce a grown virus;

harvesting said growth virus to produce a harvested virus;

purifying said harvested virus under non-denaturing conditions to produce a purified virus substantially free from cellular and serum components by:

(i) microfiltration to remove cell debris,

(ii) tangential flow ultrafiltration to remove serum components and provide a retentate,

(iii) pelleting the retentate by ultracentrifugation to further remove serum components, and

(vi) subjecting the pelleted material to sucrose density gradient centrifugation;

inactivating said purified virus with an inactivating agent selected from the group consisting of β-propiolactone, a non-ionic detergent which is n-octyl-α-D-glucopyranoside or n-octyl-β-D-glucopyranoside, and ascorbic acid, to provide a non-infectious, non-immunopotentiating and protective RS viral preparation, and

formulating said non-infectious, non-immunopotentiating and protective RS viral preparation as a vaccine.

13. The method of claim 12 wherein said tangential flow ultrafiltration is effected by employing an about 100 to about 300 kDa nominal molecular weight cutoff membrane.

14. A method of preparing a non-immunopotentiating vaccine capable of protecting a human host immunized therewith against disease caused by infection by respiratory syncytial (RS) virus, which comprises:

growing RS virus on a continuous cell line of vaccine quality to produce a grown virus;

harvesting said growth virus to produce a harvested virus;

purifying said harvested virus under non-denaturing conditions to produce a purified virus substantially free from cellular and serum components by:

(i) microfiltration to remove cell debris,

(ii) tangential flow ultrafiltration to remove serum components,

(iii) gel filtration to further remove serum components, and

(vi) ion-exchange chromatography to additionally remove serum components;

inactivating said purified virus with an inactivating agent selected from the group consisting of β-propiolactone, a non-ionic detergent which is n-octyl-α-D-glucopyranoside or n-octyl-β-D-glucopyranoside, and ascorbic acid, to provide a non-infectious, non-immunopotentiating and protective RS viral preparation, and

formulating said non-infectious, non-immunopotentiating and protective RS viral preparation as a vaccine.

15. A method of immunizing a host against disease caused by respiratory syncytial virus, which comprises administering to the host an effective amount of the vaccine composition of claim 1.

16. The method of claim 15 wherein said host is selected from infants, young children, pregnant women, women of child-bearing age, elderly individuals, immunocompromised individuals and susceptible persons.